



Case Report

Novel Agent, Sacubitril-Valsartan: Prescribing Patterns and Perceived Barriers to Hospital Formulary Inclusion

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Abstract

Purpose: Heart Failure (HF) affects approximately 5.1 million persons in America and is a major cause of morbidity and mortality. One of many federal strategies to improve care is utilization of evidence-based drug therapies. Sacubitril-Valsartan is the first in-class dual-acting angiotensin receptor neprilysin inhibitor approved by the Food and Drug Administration to reduce the risk of mortality and re-hospitalization of HF with Reduced Ejection Fraction (HFrEF) patients. Despite the positive results of the PARADIGM-HF trial, many institutions have refrained adding sacubitril-valsartan to formulary. This review investigates the barriers associated with adding the aforementioned pharmacological agent to drug formulary.

Methods: Investigators performed a search of tertiary resources, one of which was the 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. This was followed by a literature investigation utilizing PubMed and

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EMBASE for articles pertaining to sacubitril-valsartan using the inclusion terms “Entresto”, “sacubitril/valsartan”, “heart failure”, “paradigm HF”, “formulary decision” and “cost effectiveness”. Given that sacubitril-valsartan was approved in 2015, the articles were limited to the time frame of 2015-2017. The literature was ultimately selected based upon the barriers that were outlined as to why this agent has not become formulary for many institutions.

Discussion: After an initial search of sacubitril-valsartan, a total of 120 articles and studies were yielded. Following application of the inclusion and exclusion criteria, 15 were ultimately included. These articles were thoroughly dissected for information regarding formulary barriers. Ultimately, it was discovered that the most prominent barrier to approval for many institutions is the price discrepancy between standard heart failure treatment regimens and the novel agent. When comparing sacubitril-valsartan to current agents, such as enalapril, the price difference is of significance. Where enalapril costs on average \$10 a month, sacubitril-valsartan carries a price of \$460 a month. Additional barriers include administrative blockades via paperwork and authorization, as well as the risks associated with a new agent. As noted in PARADIGM-HF, symptomatic hypotension is significantly increased with this drug and that may pose a challenge of application. Patients on this medication require close monitoring and tolerance to blood pressure-lowering medications used in HF management must be accounted for through slow titration of the medication. PARADIGM-HF is currently the only completed clinical trial for sacubitril-valsartan.

Conclusion: Although sacubitril-valsartan provides a unique approach to treatment of HF, it could impose a financial burden on patients. Compared to standard HF treatment regimens, non-generics have a significantly higher acquisition cost. However, over the long-term, sacubitril-valsartan provides “a small to substantial net health benefit” over current HF medical therapy, decreasing the number of hospitalizations, resulting in decreased death from cardiovascular events. Based upon the primary literature and tertiary sources utilized, the investigators concluded that the use of sacubitril-valsartan in practice has been limited not only to cost-effective and economic dilemmas but also due to the relatively new nature of the agent, reluctance in prescribing and skepticism in clinical significance.

Introduction

Heart Failure (HF) is a major clinical syndrome characterized by symptoms of dyspnea and fatigue secondary to impaired cardiac function. HF affects approximately 5.1 million persons in the United States and is a major cause of morbidity and mortality. Although the incidence of HF has remained stable over the past several decades, the absolute mortality rate remains high at 50% within 5 years of diagnosis [1]. Due to the complexity in managing HF, it remains one of the leading causes of hospitalization among patients over 65 years of age. Older adults hospitalized with HF are at high risk for all-cause re-hospitalization, with a 1-month readmission rate of 25% [1]. Re-admissions have a substantial impact on healthcare and society. To reduce readmission rates, the Centers for Medicare and Medicaid Services (CMS) began publicly reporting 30-day risk standardization readmission rates for HF. These measures are part of a federal strategy to provide incentives to improve quality of care by reducing

preventable readmissions [2]. One of the strategies to improve quality of care is utilization of evidence-based drug therapies for managing HF.

HF can result from any structural or functional cardiac disorder that impairs the ability of ventricles to fill with or eject blood and is classified based on ejection fraction (Table 1). As cardiac output decreases, the heart relies on the following compensatory mechanisms: (1) Tachycardia and increased contractility through sympathetic nervous system activation; (2) The Frank-Starling mechanism, whereby increased preload increases stroke volume; and (3) Vasoconstriction and increased aldosterone production via the Renin Angiotensin Aldosterone System (RAAS). Although these compensatory mechanisms initially maintain cardiac function, ventricular hypertrophy and remodeling eventually manifest. The New York Heart Association (NYHA) classifies the functional incapacity of patients with cardiac disease into four levels depending on the degree of effort needed to provoke symptoms (Table 2). The American College of Cardiology Foundation/American Heart Association (ACC/AHA) Task Force on practice guidelines recommend that patients with HF should be routinely treated with a combination of pharmacological agents based on the four development stages (Table 2) [1,4-10].

Patients are at high risk for developing heart failure in ACC/AHA stage A. An Angiotensin-Converting Enzyme Inhibitor (ACEI) or an Angiotensin II Receptor Blocker (ARB) is useful for antihypertensive therapy in patients with multiple risk factors to prevent development of structural heart disease. First line therapies in patients with

structural heart disease with reduced ejection fraction (HFrEF) but no HF signs or symptoms (ACC/AHA stage B) include both ACEI or an ARB and a beta blocker. ACC/AHA stage C classifies a patient with structural heart disease and previous or current HF symptomatology [1]. If clinical evidence of volume overload exists, a diuretic is added [1,4-5]. In patients with symptomatic heart failure NYHA II-IV and ejection fraction of less than or equal to 35% or reduced ejection fraction after a myocardial infarction, the addition of an aldosterone antagonist is warranted to reduce the risk of hospitalization or death. The addition of combination hydralazine/isosorbide to standard therapy has been shown to reduce symptoms and mortality in African Americans with stage C NYHA III-IV heart failure with reduced ejection fraction. Digoxin should only be used together with standard stage C HF therapies in patients with symptomatic HF to reduce hospitalizations, but it only provides symptomatic benefits and does not improve HF survival rate [1,4-7]. Pharmacological agents targeting the RAAS have repeatedly shown to achieve HF treatment goals of improved exercise tolerance, functional class, ejection fraction and decrease mortality and hospitalization [10-13]. Despite strong evidence supporting beneficial outcomes with the use of these agents, death and readmission rates continue to remain unacceptably high. These standard drug therapies, while efficacious are associated with adverse events often leading to discontinuation of treatment. This coupled with intolerance to drug therapies, lack of education in the proper use of these agents, patient non-adherence and prescriber apathy often result in a lack of therapeutic benefit and unreasonably high rates of mortality and hospital re-admission [14].

Classification	Ejection Fraction	Description
I. Heart Failure with Reduced Ejection Fraction (HFrEF)	≤40%	Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HFrEF and it is only in these patients that efficacious therapies have been demonstrated to date.
II. Heart Failure with Preserved Ejection Fraction (HFpEF)	≥50%	Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
a. HFpEF, Borderline	41% to 49%	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patient with HFpEF.
b. HFpEF, Improved	>40%	It has been recognized that a subset of patients with HFpEF previously had HFrEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

Table 1: Classification of heart failure based on ejection fraction [1].

ACC/AHA Stages of HF		NYHA Functional Classification	
A	At high risk for HF; no identified structural or functional abnormality; no signs or symptoms	None	
B	Developed structural heart disease that is strongly associated with the development of HF but without signs or symptoms	I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea
	Underlying structural HF with current (or prior) symptoms	I, II, III or IV	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea
Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitations or dyspnea			Unable to carry out any physical activity without discomfort; Symptoms at rest
Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitations or dyspnea			
D	Advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy	IV	Unable to carry out any physical activity without discomfort; Symptoms at rest

Table 2: Classification of heart failure based on presence or absence of structural heart disease and functional capacity [1].

The RAAS and natriuretic peptides have been the focus of pharmacological targets to improve prognosis of HF patients, as over activity of these systems play a major role in the pathophysiology of the disease. Natriuretic peptides are a group of hormones which are released in HFrEF due to the activation of RAAS, fluid retention, increased preload and vasoconstriction. The activation and release of natriuretic peptides as compensatory mechanism in HFrEF leads to inhibition of the RAAS thereby reducing angiotensin II, resulting in vasodilation, antihypertensive and antiproliferative effects [15]. Neprilysin is a neuropeptidase which catalyzes break down of endogenous natriuretic peptides such as BNP, bradykinin, substance P, glucagon, etc.,. Inhibiting neprilysin leads to an increase in endogenous natriuretic peptides which in turn contributes to vasodilation, diuresis and natriuresis [14,15].

Sacubitril-valsartan (Entresto®) is the first-in-class dual acting Angiotensin Receptor Neprilysin Inhibitor (ARNI) which inhibits both neprilysin and the RAAS. Sacubitril-valsartan received approval by the US Food and Drug Administration (FDA) to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction [15]. It is recommended for use in place of an ACEI or ARB in patients with HFrEF on standard HF drug therapies. It is available as a film coated tablet in three strengths (sacubitril/valsartan): 24mg/26mg, 49mg/51mg and 97mg/103mg. The recommended starting dose is 49mg/51mg administered orally twice a day. The initial dose should be reduced to 24/26mg twice daily in patients not previously taking an ACEI or ARB or taking a low dose of these agents, in patients with severe renal impairment (eGFR <30 mL/minute/1.73m²) and in patients with moderate hepatic impairment (Child-Pugh B classification). The dose should be doubled after 2-4 weeks to the target maintenance dose of 97mg/103mg twice daily, as tolerated by the patient. Sacubitril-valsartan is contraindicated with concomitant use of an ACEI or ARB. If switching from an ACEI to sacubitril-valsartan then a washout period of 36 hours between administrations of the two drugs is recommended. The use of sacubitril-valsartan is contraindicated in patients with previous history of angioedema from an ACEI or ARB therapy and with concomitant use of aliskiren in patients with diabetes [16].

Sacubitril-valsartan was approved after several neprilysin inhibitors, studied alone or in combination with ACEI failed to show overall improved outcomes. Omapatrilat was the first drug studied for its dual inhibition of neprilysin and ACE. Initial results of omapatrilat were promising in lowering blood pressure and improving hemodynamics in patients with HF; however, there was an increased incidence of angioedema reported likely due to the increase in bradykinin from inhibition of three proteases, neprilysin, ACE and aminopeptidase [17,18]. Due to the high occurrence of angioedema noted in clinical trials, omapatrilat did not receive FDA approval. Fortunately, this paved way to finding the right combination of drug classes which would provide the same beneficial effects noted with omapatrilat without the increased incidence of angioedema. This led to the development of valsartan-sacubitril which includes an ARB instead of an ACE, therefore reducing the risk of angioedema. Combining inhibition of the RAAS and neprilysin augments the beneficial natriuretic peptide pathway while providing direct antagonism to increase angiotensin II [19].

Sacubitril-valsartan was studied in a handful of hypertension, HFrEF and HFpEF clinical trials [11,20,21]. The pivotal HFrEF trial which led to the approval of sacubitril-valsartan is the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF). This was a double-blind, prospective, randomized controlled trial designed to test superiority of sacubitril-valsartan compared to enalapril in improving morbidity and mortality in patients with HFrEF. Enalapril was selected as the comparator drug as it is considered the gold standard of care in HF patients with this classification. Patients were enrolled in the PARADIGM-HF trial if they had an EF of less than or equal to 40% (which was later changed to less than or equal to 35%) and NYHA II-IV symptoms, BNP of at least 150pg/mL or NT-proBNP level greater than or equal to 600pg/mL or BNP of at least 100pg/mL or NT-ProBNP greater than or equal to 400pg/mL if hospitalized due to HF in the last 12 months [11]. The primary endpoint was composite of cardiovascular death or first hospitalization for HF. Secondary outcomes included time to death from any cause, change from baseline in the Kansas City Cardiomyopathy Questionnaire (KCCQ) score at 8 months, time to new-onset atrial fibrillation and time to decline in renal function which was defined as end-stage renal disease or a decrease in eGFR of at least 50% or a decrease of more than 30mL/minute/1.73 m² or less than 60mL/minute/1.73 m² [11]. PARADIGM-HF trial used a unique study design which comprised of a single-blind active run-in phase to ensure study participant tolerated both the study drugs followed by a double-blind phase where patients were randomized into one of the two treatment arms. The single-run in phase provided the data and safety monitoring committee with information related to the safety of sacubitril due to limited experience with the use of this drug in HF patients. The study enrolled 10, 521 patients who entered the initial single-blind run-in phase of the trial which comprised of 2 weeks of treatment with enalapril 10mg twice daily dose. After completion of this 2-week run-in phase, 9,419 patients entered the second single-blind run-in phase which consisted of 4 weeks of treatment with sacubitril-valsartan. After completion of the second run-in phase, 8,442 patients underwent randomization in a double-blind fashion. After excluding 43 patients due to invalid randomization and site closure from violation of Good Clinical Practice (GCP), 4,187 patients were assigned to sacubitril-valsartan group and 4,212 patients were assigned to the enalapril group. The study was designed to detect a 15% relative reduction in cardiovascular related death in patients treated with sacubitril-valsartan. The study was planned for duration of at least 34 month; however, it was stopped early because of significant reduction in both primary endpoint and cardiovascular death seen in the sacubitril-valsartan arm at median follow-up of 27 months. The primary composite outcome of cardiovascular death or first hospitalization for HF occurred in 21.8% of patients treated with sacubitril-valsartan and 26.5% patients treated with enalapril (HR 0.80, 95% CI, 0.73-0.87; p<0.001). Secondary outcome of death from any cause was significantly reduced in sacubitril-valsartan group compared to enalapril group (17.0% vs. 19.8%, HR 0.84, 95% CI 0.76-0.93, p<0.001). A lower mean decrease in KCCQ score at 8 months was also noted in sacubitril-valsartan group when compared to enalapril (2.99 points vs. 4.63 points, mean difference 1.64, 95% CI 0.63-2.65, p=0.001). The incidence of new onset atrial fibrillation was similar in both study groups (3.1% vs. 3.1%). A decline in renal function occurred in 2.2% of patients in the sacubitril-valsartan group compared to 2.6% of patients in the enalapril group (p=0.28) [11].

Although the inclusion criteria listed NYHA II-IV symptoms, 5% of the study participants had NYHA I symptoms. It was noted that the reduction in risk of primary composite outcome was lower in patients with NYHA I and II symptoms as compared to patients with NYHA III and IV symptoms. There was no difference in other pre-specified subgroups defined as age, sex, race, region, eGFR, diabetes, systolic blood pressure, ejection fraction, atrial fibrillation, NT-proBNP levels, hypertension, prior use of ACEI or aldosterone antagonist, previous hospitalization from HF and time since diagnosis of HF. Safety outcomes were similar in the two treatment groups in regards to angioedema (0.5% vs. 0.2%) with 3 patients in the sacubitril-valsartan group compared to 1 patients in the enalapril group requiring hospitalization with no airway compromise ($p=0.31$). Other safety issues such as hypotension were more common in the sacubitril-valsartan group (14.0% vs. 9.2%, $p<0.001$) which often led to discontinuation of treatment. Overall, patients in the sacubitril-valsartan group tolerated the drug well with 11.3% vs. 14.3 % ($p<0.001$) of patients reporting cough and 11.3% vs. 14.3% ($p=0.07$) of patients developing hyperkalemia (serum potassium > 6 mmol/L).

The results of the PARADIGM-HF study showed impressive results of reduction in cardiovascular death and heart failure hospitalization in patients treated with sacubitril-valsartan which may be a safe alternative to ACEI or ARB in patients with HFrEF managed on standard drug therapies [11]. Symptomatic hypotension was significantly increased in the PARADIGM-HF trial which may pose a challenge in the use of this drug. Close monitoring and consideration of patients' tolerance to the combination of blood pressure lowering medications used in management of HFrEF as well as slow titration after initiation of this drug is crucial. There is no evidence that sacubitril-valsartan should replace beta blockers or aldosterone antagonist in patients with HFrEF. Due to the potent blood pressure lowering effect of this agent, it can be considered for use in patients with resistant hypertension and HFrEF.

Despite the positive results of this landmark trial in comparing Entresto® to standard therapy, many institutions have still refrained from adding this agent to their formulary systems. The primary objective of this study was to investigate the potential barriers and clinical challenges associated with prescribing this novel agent in clinical practice.

Methods

Literature database searches were performed with the goal of understanding the post-marketing strategies, barriers of prescription attainment, cost-effective analysis and overall decision-making psychology. Investigators first conducted a search of tertiary sources to obtain information regarding the management of HF and included a focus on the 2017 ACC/AHA/HFSA update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. After this initial search, a primary literature search was performed utilizing PubMed and EMBASE. Inclusion criteria incorporated the terms "Entresto", "Sacubitril/valsartan", "Paradigm HF", "Formulary Decision", "Clinical Challenges" and "Cost-Effectiveness". With respect to exclusion criteria, due to the fact that sacubitril-valsartan was approved in 2015, articles were limited to the time frame between 2015-2017. The literature was ultimately selected based upon the previous defined inclusion criteria, the economic impact of Entresto® and the barriers associated with the delay in the clinical application of this drug combination. Any articles discussing the possibilities to another disease state other

than congestive heart failure patients with reduced ejection fraction is excluded. Furthermore, articles regarding the use of Entresto® in other trials rather than the PARADIGM-HF Trial were also excluded.

The following MeSH term combinations yielded a total of 504 articles across both databases. All the results were extrapolated to a Microsoft Excel documents where the repeated articles in both databases were filtered out. A total of 204 articles remained as raw material to be analyzed. After the application of the inclusion and exclusion criteria, a total of 180 articles remained. Ultimately, 14 articles were applied to fill the purpose of our argument.

Literature Review

Cost-effective evaluation

Gaziano, et al., addressed, "In a given year, 1000 patients receiving sacubitril-valsartan would cost approximately \$4.4 million more in differential drug costs". Monthly costs for sacubitril-valsartan were \$317 versus \$0.96 for enalapril. However, "in the same year, reductions in hospitalizations lead to savings of \$1.3 million compared with patients receiving enalapril. This model-based analysis suggested health benefits associated with the agent when compared to standard treatment were cost-effective at "commonly accepted willingness-to-pay of \$50,000 per Quality-Adjusted Life-Year (QALY) gained". The results also exhibited a result of more than a year of life gained and significant cost-savings because of the avoided hospitalizations [22].

The cost-effectiveness analysis by King, et al., used the Markov model to compare sacubitril-valsartan with enalapril. It was concluded that after evaluating costs, benefits and cost-effectiveness over a 40 year time horizon, sacubitril-valsartan was more expensive overall than enalapril. Patient gained an average of 9.48 years of life (6.59 QALYs) added to their diagnosis with the use of sacubitril-valsartan as compared to 8.40 years (5.83 QALYs) on enalapril. Prices for the medications were compared and yielded the conclusion that enalapril (or any ACEI) would be less expensive for patients to obtain as compared to sacubitril-valsartan. The difference lied in the benefits the drug proposed and the authors stated that, "At the current price, the use of sacubitril-valsartan to reduce HF hospitalizations is unlikely to be cost saving. Benefits of increased quantity and quality of life may be cost-effective depending on Willingness to Pay (WTP)" [23].

The authors Langley, et al., stressed the fact that the differences in costs between sacubitril-valsartan and enalapril were greatly marked in their study. "The per-patient cost in the Entresto® arm was 23.6% higher than for those on the ACE I for the survival estimates". After what the authors called an "imaginary simple decision analysis", it was suggested a 90% price reduction for the combination drug. The authors concluded "The most perplexing feature of the Institute for Clinical and Economic Review (ICER) assessment of Entresto® for heart failure hospitalization is how a product that is over 120 times as expensive as the ACEi standard of care in surviving patients with heart failure can be considered to be cost-effective". The authors also stated that, since the ICER Entresto® model, "which is the standard reference case for quality adjusted life years found in the drug evaluation reports," was not released for public review it was impossible to "review, modify and replicate" and that it then cannot be used to support formulary decisions" [24].

The therapeutic challenges

Packer, et al., stressed the importance of “utilizing new pharmacotherapy agents that have conclusive positive data and that will, ultimately, optimize the quality of life and continuance” and stated “while sacubitril-valsartan is still a new novel therapeutic agent for the treatment of chronic heart failure with NYHA Class 2-4 heart failure, there are still primary care physicians who would avoid prescribing the agent regardless of the clinical support in the literature”. The author concluded that “there is no excuse on the avoidance to use the new pharmacologic agent and by refraining, it can inadvertently lead their patients in one of the top causes of heart failure mortality, sudden cardiac death” [25].

O'Connor, et al., explains how the implementations of “break-through therapies transcend from the positive numbers in controlled clinical trials” and indicates that “while the improvement of quality of life and reduction of mortality was concluded from the PARADIGM-HF trial, the slow rise in the use of Entresto® is multifactorial including physicians being traditional with seasoned, low cost and effective pharmaco-interventions; patient’s involvement; approvals of insurances; and medical sponsor. The lack of physicians refraining from the use of Entresto® also results in a chain reaction where other physicians will also abstain from using Entresto®. With the lack of documentation in the non-controlled environment and special populations and populations not studied in the clinical trial, many physicians will not be comfortable using novel drugs and breaking the ice [26].

Packer, et al., metaphorically uses a Nobel Prize-winning novel to compare conventional heart failure interventions with new break-through agents. “While the use of ACEI/ARBs have proven to be the corner-stone treatment with their appearance, there are limitations in their usage. As time has gone by and the addition of therapeutic agents that further optimize heart failure therapy is seen, the concerns from the limitation of ACEI/ARBs have been overlooked. The Assessment of Treatment with Lisinopril and Survival (ATLAS) and Heart Failure Endpoint Evaluation of Angiotensin 2 Antagonist Losartan (HEAAL) trails have demonstrated that increasing the dosage of ACEIs and ARBs do not provide clinically significant improvement in the reduction of mortality. Additionally, the up-titration of the conventional renin-angiotensin system blockade agents often comes with an increased risk of hypotension, angioedema, hyperkalemia and renal insufficiency. Ultimately, the benefits do not outweigh the risk and it often leads to discontinuation or reversing the increments of the dosage”. While exposing the limitation of conventional renin-angiotensin system blocking agents, the authors resumed to referring to sacubitril-valsartan as a “new method” to block this system. While supporting the positive results of Entresto® in the PARADIGM-HF results, the authors explain how this new agent covers the limitations of ACEI/ARBs. “Patients, in the PARADIGM-HF trial, randomized to the Entresto® arm experienced a better tolerance and required less dose reduction than the enalapril arm. On the other hand, results showed that those patients who had a dose titrated down based on their tolerance had an increased risk of mortality compared to those who were able to sustain the higher doses” [27].

Discussion

Following the positive results of the PARADIGM-HF trial, the introduction of Entresto® to the market was expected to be of significant impact to the management of HFREF. However, the use of this

novel agent has been idled since the agent’s approval. The primary outcome in the PARADIGM-HF trial had shown significant reduction of re-hospitalization and mortality with Entresto®. However, its use is being suppressed due to numerous factors; the main concern being financial. While some physicians, medical sponsors and health insurances compare conventional RAAS inhibitory agents to Entresto®, the price difference is “several tenth fold”. Regardless of its high-costs, Entresto® has been clinically and financially warranted through the assessment of cost-effective and economic analysis whereby in reducing re-hospitalizations, there will ultimately be a decrease in direct as well as indirect costs to the overall health care system with numbers exceeding millions of dollars.

The price of this novel agent is presumed to be its highest barrier to clinical application. Nonetheless, there are several cost-effective analyses that can prognosticate the net benefit when an ARNI is used appropriately. The use of Entresto® transcends beyond the economic evaluation and the positive impact on patient’s outcome and quality of life as supported by the PARADIGM-HF trial. Perhaps, there are subjective rationales in the selection of conventional drug management rather than the emergent one. Conceivably, physicians are more comfortable with their use, cost, effectiveness, efficiency and results of what was once the cornerstone of HF management. In addition, the risk rates of angioedema in the unexplored communities as well as the inexperience in using a new class of pharmacotherapy also play key roles. Lastly, patients with economic burden or no health insurance at all must also be factored into place. Physicians, in their own discretion, have the authority to abstain from using a novel drug. While there has been a slow rise in the prescribing of Entresto® since its approval, the lack of documentation and knowledge about the agent further raises the barriers to formulary and its use in practice, and introduces new ethical dilemmas in the management of HFREF. Meanwhile, the outcome of patients hospitalized for an acute HF episode remains unacceptably high post-discharge and re-hospitalization rates with conventional RAAS blocking agent [28].

Conclusion

Based upon the primary literature and tertiary sources utilized, the investigators concluded that the use of sacubitril-valsartan in practice has been limited not only to cost-effective and economic dilemmas but also due to the relatively new nature of the agent and skepticism in clinical significance. Conventional RAAS blocking agents have a long history of being proven safe, effective and affordable for patients. With respect to the nature and reluctance in prescribing, it was concluded based on this literature review that physicians are more familiar with the safety and efficacy of ACEI and ARB standard therapies and thereby replacing these medications may result in unnecessary and uncertain outcomes. Consequently, physicians feel more confident in prescribing agents supported with a voluminous background of clinical efficacy compared with an agent that is newly introduced to the market. With regards to cost, the price of sacubitril-valsartan is approximately \$317/month versus \$0.96/month for enalapril. This extreme price discrepancy may cause significant hesitance in prescribing or having the agent authorized for coverage by third party insurance plans. Moreover, we concluded that in its pursuit for formulary approval Entresto® faces barriers of a multifactorial nature, mainly expenditures and therefore it may be a prolonged period of time before widespread usage occurs. The recently published TRANSITION trial in 2018 comparing in-hospital versus post-discharge initiation of

sacubitril-valsartan in HFrEF patients may modify prescribing patterns moving forward.

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